

US005888552A

United States Patent [19]

Bounous et al.

[11] **Patent Number:** 5,888,552

[45] **Date of Patent:** Mar. 30, 1999

[54] ANTI-CANCER THERAPEUTIC COMPOSITIONS CONTAINING WHEY PROTEIN CONCENTRATE

[75] Inventors: Gustavo Bounous, Monteal; Phil Gold,

Westmount, both of Canada

[73] Assignee: Immunotec Research Corporation

Ltd., Quebec, Canada

[21] Appl. No.: **381,975**

[22] PCT Filed: Aug. 5, 1993

[86] PCT No.: PCT/CA93/00309

§ 371 Date: May 8, 1995

§ 102(e) Date: May 8, 1995

[87] PCT Pub. No.: **WO94/04168**

PCT Pub. Date: Mar. 3, 1994

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 929,347, Aug. 13, 1992, abandoned, and Ser. No. 866,756, Apr. 10, 1992, Pat. No. 5,456,924, which is a continuation-in-part of Ser. No. 417, 246, Oct. 4, 1989, Pat. No. 5,290,571, which is a continuation-in-part of Ser. No. 289,971, Dec. 23, 1988, abandoned, which is a continuation-in-part of Ser. No. 188,276, Apr. 29, 1988, abandoned, said Ser. No. 929,347, is a continuation-in-part of Ser. No. 417,246.

426/72

[56] References Cited

U.S. PATENT DOCUMENTS

4,784,685 11/1988 Meister 504/110

FOREIGN PATENT DOCUMENTS

222560 5/1981 Argentina . 1495940 12/1977 United Kingdom .

OTHER PUBLICATIONS

Anderson, M.E., "Tissue glutathione", C.R.C. Handbook of Methods for Oxygen Radical Research, pp. 317–329 (1985) (Exhibit 1).

Lauterburg, B.H. et al., "Therapeutic doses of acetaminophen stimulate the turnover of cysteine and glutathione in man", *J. Hepatol.*, vol. 4, pp. 206–211 (1987) (Exhibit 2). Lewis, A.D. et al., *Proc. Natl. Acad. Sci.*, vol. 85, pp. 8511–8515 (1988) (Exhibit 3).

Russo, A. et al., "Selective modulation of glutathione levels in human normal versus tumor cells and subsequent differential response to chemotherapy drugs", *Cancer Res.*, vol. 46, pp. 2865–2848 (1985) (Exhibit 4).

Walstra, P.J., "Dairy Chemistry and Physics", Wiley J. Nitork, (ed.), p. 106 (1984) (Exhibit 5).

Williamson, J.M. et al., "Intracellular cysteine delivery system that protects against toxicity by promoting GSH synthesis", *Proc. Natl. Acad. Sci. U.S.A.*, vol. 79, pp. 6246–6249 (1982) (Exhibit 6).

Bounous, G., et al., "Dietary Whey Protein Inhibits the Development of Dimethylhydrazine Induced Malignacy." Clin. Invest. Med., (1980) vol. 11, pp. 231–217.

Papenburg, R., et al., "Dietary Milk Proteins Inhibit The Development of Dimethylhydrazine–Induced Malignacy." *Tumor Biology*, (1990) vol. 11, pp. 129–136.

Baruchel, S., et al., (1992) AACR Abstract, "Different Effects of OTZ on Organ GSH Levels in Rate Bearing Tumors".

John, A.M, et al., "Amino Acid Requirements of the Growing Mouse." J. Nutr., (1976) vol. 106, pp. 1361–1367.

Hoag, W.G., et al., "Nutrition" In: *Biology of the Laboratory Mouse*, E.L. Green, (ed.), (McGraw-Hill, New York: 1966) pp. 39-43.

Cunnigham, A., et al., "Further Improvements in the Plaque Technique for Detecting Single Antibody Forming Cells." *J. Immun.*, (1968) vol. 14, pp. 559–600.

Anderson, M.E., "Tissue Clutathione" In: Handbook of Methods for Oxygen *Radical Research*. (C.R.C. Press, Boca Raton: 1988) pp. 317–329.

Raton: 1988) pp. 317–329. Glatt, H., et al., "Mutagenicty of Glutathione and Cysteine in the Ames Test." *Science*, (1983) vol. 220, pp. 961–962. Taylor, Y.C., et al., "Elevation of Intracellular Glutathione Levels Following Depletion and its Relationship to Protection Against Radiation and Alkylating Agents." *Pharmacol. Ther.*, (1988) vol. 39, pp. 293–299.

White, C.W., et al., "Hypoxia Increases Glutathione Redox Cycle and Protects Rat Lungs Against Oxidates." J. Appl. Physiol., (1988) vol. 65, pp. 2607–2616.

Anderson, M.E., et al., "Transport and Direct Utilization of Gamma–Glutamylcyst(e)ine for glutathione Sythesis." *Proc. Natl. Acad. Sci. U.S.A.*, (1983) vol. 80, pages 707–711. Richie, J.P., et al., "Correction of a Glutathione Deficiency in the Aging Mosquito Increses its Longevity." *Proc. Soc. Exp. Biol. Med.*, (1987) vol. 184, pp. 113–117.

Fernandez-Checa, J.C., et al., "Effects of Chronic Ethanol Feeding on Rat Hepatocyte Glutathione." *J. Clin. Invest.*, (1989) vol. 83, pp. 1247–1252.

Meister, A., et al., "Glutathione." Ann. Rev. Bloch., (1983) vol. 52, pp. 711-760.

Hamilton, T.C., et al., "Augmentation of Adriamycin, Melphalan and Cisplastin Cytoxicity in Drug Resistant and Sensitive Human Ovarian Cancer Cell Lines by BSO Mediated GSH Depletion." *Biochem. Pharm.*, (1985) vol. 34, pp. 2583–2586.

(List continued on next page.)

Primary Examiner—Jean C. Witz Attorney, Agent, or Firm—John P. White; Cooper &

Attorney, Agent, or Firm—John P. White; Cooper & Dunham LLP

[57] ABSTRACT

This invention relates to a method of treatment of patients having lesions resulting from cancer cells and to an application as an anti-cancer composition of undenatured whey protein concentrate.

22 Claims, 3 Drawing Sheets